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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,908	08/01/2005	Bernd Kuhn	Le A 36 031	7332

35969 7590 05/18/2010

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
05/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,908	KUHN ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Remarks, filed 4 Mar 2010. No claims are amended.

This application is the national stage entry of PCT/EP03/03327, filed 31 Mar 2003; and claims benefit under 35 USC 119(a-d) of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002; currently an English language translation of this foreign priority document is of record and the claim of foreign priority has been perfected.

Claims 1-18 are pending in the current application and are examined on the merits herein.

The following grounds of rejection are reiterated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8, 9 and 11-17 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004).

Mittendorf discloses a pharmaceutical composition comprising the compound (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (column 199, claim 1 and column 200, claim 5). Mittendorf discloses the compound is a cannabinoid receptor agonist (column 1, lines 23-50). This composition is suitable for administration as a continuous infusion (column 36, lines 55-58). Mittendorf discloses the composition wherein the solvent is aqueous NaCl (column 36, lines 15-20). Mittendorf discloses the compound with suitable excipients and envisions the use of organic solvents as auxiliary solvents if water is used as a diluent (column 37, lines 20-30). Mittendorf discloses the dosage of the compound of 0.01 to 10 mg/kg (column 37, lines 35-37).

Mittendorf does not specifically disclose the excipient cyclodextrin or the ratio of compound to cyclodextrin.

Szabo teaches that an aqueous solution diluted with a 19% cyclodextrin solution is a suitable vehicle for infusing the cannabinoid receptor agonists, WIN 55,212-2 and CP 55,940. See page 820, 2nd paragraph under "Drugs." The reference further teaches that other similar drugs are dissolved in ethanol and saline.

Liu teaches the technique of solubility enhancement by applications of cyclodextrin is well known (page 111, paragraph 1). Liu teaches the structural aspects of complexation largely depends on the complexed compound's size compatibility with the dimensions of the CD cavities (page 115, especially paragraph 1). Liu teaches it is routine optimization of concentration of CD to form 1:1 or 2:1 CD:guest complex. (page 116, paragraph 2). Liu teaches many examples are known to demonstrate the effect of CD on solubility, dissolution rates, and bioavailability of poorly water soluble compounds (page 126, paragraph 5 at bottom of page) as well as by mechanisms not requiring complexation by altering the lipid barrier at the absorption site (page 127, paragraph 2). Liu teaches known advantages of CD inclusion for solid preparations for content uniformity, liquid preparations are improved solubility and stability, and for injectable preparations reduction of drug-induced hemolysis and muscular tissue damage, and ease of formulating solid preparations into liquid preparations (page 127, at bottom of page and page 128, 5. Injectable Preparations at middle of page).

Loftsson et al. teaches it is well known that the pharmaceutical applications of cyclodextrin are for drug solubilization and stabilization. Loftsson et al. teaches the

methods of preparing drug-cyclodextrin complexes are known to be routine in the art and well within the level ordinary skill in the art (page 1020, left column, paragraph 2). Loftsson et al. teaches it is routine in the art to optimize the concentration of cyclodextrin, teaching examples of 1.5, 10, 15 and 50 %w/v, (page1021, table 5 at top of page). Loftsson et al. teaches molecules may also form complexes with drug molecules like peptides and proteins that is qualitatively different from the complexes with small molecular weight compounds, with the maximum benefit obtained at low cyclodextrin concentrations and the benefits are only partly concentration dependent (page 1024, left column, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. One of ordinary skill in the art would be motivated to combine Mittendorf in view of Szabo et al and Liu and Loftsson et al. because Mittendorf et al. suggests the compound of Mittendorf et al. is water-insoluble requiring organic solvents as auxiliary solvents if water is used as a diluent and Liu and Loftsson et al. teach it is well known that cyclodextrin is used to improve solubility of water-insoluble compounds. Further, one of ordinary skill in the art would be motivated to select cyclodextrin as the agent used to improve solubility of water-insoluble compounds because Szabo et al, drawn to infusing the cannabinoid receptor agonists as compositions comprising cyclodextrin, suggests the use of a known technique to improve similar products in the same way. Liu and Loftsson teach it would have been routine experimentation for one of ordinary

skill in the art to optimize the concentration of cyclodextrin within the range of 1.5 to 50 % w/v based on the amount of guest compound.

Response to Applicant's Remarks:

Applicant's Remarks, filed 4 Mar 2010, have been fully considered and not found to be persuasive.

Applicant asserts that Liu and Loftsson do not provide reasonable predictability of success and therefore do not provide an enabling methodology. MPEP 2143.02 provides "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)". Applicant notes that Liu and Loftsson doe not teach absolute predictability. However as stated *In re Rinehart* absolute predictability is not required under 35 U.S.C. 103(a). Moreover, as detailed in the rejection above, Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. as taught in Liu and Loftsson et al. provide at least some degree of predictability. Applicant provides no evidence showing there was no reasonable expectation of success.

Applicant notes that Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. does not explicitly teach a detailed enabling methodology. However, Loftsson et al. teaches the methods of preparing drug-cyclodextrin complexes are known to be routine in the art and well within the level ordinary skill in the art (page 1020, left column, paragraph 2). As provided by MPEP 2141 II.C., "The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the

time of the invention." Therefore a person of ordinary skill in the art is presumed to have known the relevant art at the time of the invention regarding methods of preparing drug-cyclodextrin complexes known to be routine in the art. Further, MPEP 2164.01 provides "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)".

Claims 1-9 and 11-18 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000).

Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. teach as set forth above.

The references are silent regarding the pH of the solutions or the use of citric acid.

Nakazi teaches that a citrate buffer (pH 4.8) is a suitable vehicle for cerebral infusion of the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See paragraph bridging pages 20 and 21.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said compound for infusion

using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further obvious to modify this composition by adjusting it to a suitable pH for cerebral infusion with a citrate buffer with a reasonable expectation of success.

The instant claims recite a composition comprising compound (I) and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 4 Mar 2010, have been fully considered and not found to be persuasive.

Applicant's remarks regarding a reasonable predictability of success and an enabling methodology with regard to the teaching of Liu and Loftsson et al. as applied in the rejection is addressed as above.

Claims 1-4 and 8-17 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004) and Yamada (US 5,807,337, of record).

Mittendorf et al. in view of Szabo et al. and Liu and Loftsson et al. teach as set forth above.

The references teach the infusion of cannabinoid receptor agonists but are silent regarding the description of the infusion apparatus used in each reference.

It is well known in the art to use an infusion apparatus for the continuous administration of therapeutic agents, and the drug-contacting surfaces are typically plastic. See, for example, Yamada at col 5, lines 15-25.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the recited composition, as set forth above. It would be further obvious to combine the composition with an infusion apparatus to form a kit for administration of the composition. It would be within the scope of the artisan to select any appropriate apparatus for this utility.

Response to Applicant's Remarks:

Applicant's Remarks, filed 4 Mar 2010, have been fully considered and not found to be persuasive.

Applicant's remarks regarding a reasonable predictability of success and an enabling methodology with regard to the teaching of Liu and Loftsson et al. as applied in the rejection is addressed as above.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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